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(54) Title: TOPICAL PHARMACEUTICAL COMPOSITIONS COMPRISING PROANTHOCYANIDINS FOR THE TREATMENT OF DERMATITIS

(57) Abstract: Pharmaceutical compositions for the topical administration, comprising as active ingredients proanthocyanidins alone or combined with glycyrrhetinic acid, telmesteine, alpha-bisabolol or other components having complementary activity, in admixture with a suitable carrier, useful for the treatment of avariety of pathologies such as atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis, radiation dermatitis, psoriasis, xerosis and atopia as well as for the treatment of mucosae inflammatory conditions.

TOPICAL PHARMACEUTICAL COMPOSITIONS COMPRISING PROANTHOCYANIDINS FOR THE TREATMENT OF DERMATITIS

The present invention relates to pharmaceutical compositions for the topical administration comprising as active ingredients proanthocyanidins, glycyrrhetinic acid and telmesteine, in admixture with a suitable carrier.

The topical pharmaceutical compositions of the present invention are useful for the treatment of inflammatory conditions of the skin, such as atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis, radiation dermatitis, psoriasis, xerosis and atopia as well as of mucosae and eye inflammatory conditions.

Dermatites are superficial skin inflammations, characterized by vesicles, erythema, edema, oozing, scaling or crusting lesions and intense itching. Various types of dermatitis exist: contact dermatitis, which can be caused by irritants with which the skin is in contact or by non-irritating substances to which the subject is allergic; atopic dermatitis, a chronic disease characterized by strong itching; seborrheic dermatitis, a scaling disease which mainly affect the face and scalp. In principle, the treatment consists in removing the offending agent, which however cannot in many cases be identified or removed. Treatment is therefore based on corticosteroids, which have however well known side-effects: they reduce the immune defenses, which can induce infections, mainly by fungi or Candida; suspension of the treatment should be gradual; they cannot be used during the acute oozing phase; a rebound effect may appear on stopping treatment. Furthermore, corticosteroids should not be used for prolonged treatments, particularly in children, since they can give rise to systemic effects.

In the case of seborrheic dermatitis, alternative treatments, based on hydrogenated vegetable oils or hydrophilic petrolatum, or medicated

shampoos (based on zinc-pirithione, selenium sulfide, sulfur and the like) in are not resolutive.

In case of the mucosae inflammatory conditions, in particular of mouth, gingival, rectal, vaginal and eye mucosae, a number of topical treatments are available, including the use of steroidal or non-steroidal antiinflammatory agents, with the problems and side effects characteristics for these medicaments.

Different uses of proanthocyanidins have been described in the pharmaceutical and cosmetic fields. EP 0 694 305 discloses topical compositions of proanthocyanidins combined with coumarins (esculoside and the like) for the treatment of peripheral vasculopathies, such as bedsores, scars, couperose, varices and the like. US 5,470,874 describes a combination of proanthocyanidins and vitamin C for the topical use, as sunscreen, for stimulating collagen synthesis and for restoring damaged collagen. Finally, JP 6,336,421 relates to topical formulations of proanthocyanidins combined with anti-inflammatories, among which glycyrrhetinic acid and derivatives are cited, for the cosmetic use and against sunburns. However, to date the use of proanthocyanidins in the treatment of pathologies such as chronic dermatitis, seborrheic dermatitis and allergic dermatis has not been described.

Proanthocyanidins are widely diffused in a number of vegetable species. They are vegetable extracts containing bioflavonoids, with well-defined chemical profile, consisting for about 15% of dimers, about 20% of trimers and tetramers, and of small amounts of catechin and epicatechin. Proanthocyanidins exert both skin protecting action from the aggression by free radicals and restoration action of the damages to the skin structure through stimulation of collagen production. They also contain essential fatty acids similar to those of the skin hydrolipidic barrier, which contribute to keep said barrier intact. Finally, proanthocyanidins reduce the concentration of enzymes such as elastase, collagenase, hyaluronidase and beta-glucuronidase, which are

responsible for the destruction of elastin, collagen and hyaluronic acid proteins. Therefore, proanthocyanidins are widely used in the pharmaceutical and cosmetic industries, thanks to their restoring, regenerating, nutrient and restructurant actions, which restores the skin elasticity and tonicity.

According to the present invention, the proanthocyanidins extracted from grape seeds and skin of *Vitis vinifera* are particularly preferred. Most preferred are the complexes of proanthocyanidins from *Vitis vinifera* with phospholipids, prepared according to the process disclosed in US 4,963,527.

18-β-Glycyrrhetinic acid, extracted from the roots of *Glycyrrhiza glabra*, is known to have antiinflammatory properties on the skin, in particular in case of burns and redness.

Telmesteine (N-carbethoxy-4-thiazolidinecarboxylic acid) exerts antiradicalic and protective action against the oxidizing agents responsible for skin damages, as well as inhibiting elastase and collagenase actions.

The topical pharmaceutical compositions of the present invention will contain the active ingredients in admixture with a suitable carrier, preferably a carrier rich in polyunsaturated fatty acids. According to the invention, suitable carriers comprise squalene, fatty acids, fatty acids esters, vegetable oils, natural or synthetic triglycerids. More preferably, suitable carriers comprise squalene, karité butter, octyl palmitate and oenothera oil.

In particular, karité butter (also known as shea butter) is a fat consisting of a mixture of saturated and unsaturated fats, extracted from the seeds of *Butirospermum parkii*, a tree from northern Africa, which is used in cosmetics thanks to its protective and softening actions, which make it particularly useful for sensitive skins as well as for skins which easily redden.

Oenothera oil (also known as evening primrose oil), extracted from the plant *Oenothera biennis*, is rich in essential polyunsaturated fatty acids, in particular γ-linolenic acid, indispensable for regenerating the skin and all

cellular tissues.

According to a preferred embodiment, the pharmaceutical compositions of the invention will further contain compounds with antioxidizing activity, such as tocopherols and ascorbic acid or esters thereof, preferably tocopherol acetate and ascorbyl palmitate or tetrapalmitate, to further increase the protective effect on cell membranes and to slow down the oxidation of polyunsaturated fatty acids.

The compositions of the present invention may further contain other active ingredients, with complementary or anyway useful actions in the treatment of dermatosis.

Examples of said active ingredients are:

- salicylic acid, which exerts a keratolytic action useful for the treatment of seborrheic dermatitis;
- hyaluronic acid, which is useful for the treatment of radiation dermatitis due to its hydrating and healing action;
- alpha-bisabolol, one of the active principles present in chamomile essential oil (Matricaria flos), which has lenitive and anti-redness action;
- zinc pidolate, which exerts slightly astringent, emollient and lenitive actions, blocks and prevents the formation of free radicals thanks to its competitive action towards iron ions, and is active in the enzymatic processes of skin metabolism;
- allantoin which has astringent, slightly keratolytic and healing actions;
- moisturizers or wetting agents;
- piroctone olamine (octopirox), a known agent with antiseborrhoic activity.

Therefore, a further preferred embodiment relates to the pharmaceutical compositions of the invention also containing salicylic acid, for the treatment of seborrheic dermatitis.

A further preferred embodiment relates to the pharmaceutical

compositions of the invention also containing hyaluronic acid, for the treatment of radiation dermatitis.

A further preferred embodiment relates to the pharmaceutical compositions of the invention also containing alpha-bisabolol and allantoin.

A further preferred embodiment relates to the pharmaceutical compositions of the invention also containing zinc pidolate.

The topical pharmaceutical compositions of the present invention can be in the form of cream, gel, lotion, suspension, spray, ointment, foam.

The topical pharmaceutical compositions of the present invention will contain the active ingredients in the following concentrations (w/w):

a) proanthocyanidins in the form of complexes with phospholipids: 0.01% to 1%;

b) glycyrrhetinic acid: 0.1 to 5%, preferably 1 to 2%;

c) telmesteine: 0.01% to 1%; and

- carriers (squalene, karité butter, octyl palmitate and oenothera oil): 10-50%;
- antioxidants (tocopherol acetate 0.5-5%; ascorbyl palmitate 0.01-0.1%);
- salicylic acid 0.1-5%;
- hyaluronic acid 0.1-10%;
- alfa-bisabolol 0.1-3%;
- zinc pidolate 0.01-1%;
- allantoin 0.1-2%.

The daily dosage will be determined by the physician; by way of example, it will consist of one or more daily applications even for protracted times.

Some examples of formulations according to the present invention are shown hereinafter.

Example 1

CREAM

Complexes of proanthocyanidins from *Vitis vinifera* with phospholipids	0.100
Glycyrrhetinic acid	0.800
Telmesteine	0.100
Octyl palmitate	7.000
Pentylene glycol	5.000
Karité butter	4.000
Arachidyl alcohol, behenyl alcohol, C 12-20 alkylglucoside	4.000
Glyceryl stearate and glyceryl (100) OE stearate	3.000
Oenothera oil	2.000
Capriloyl glycine	1.500
Bisabolol	1.200
Vitamin E acetate	1.000
Carbomer	0.700
Octyl glycerin	0.600
Salicylic acid	0.500
Octopirox	0.500
Sodium hydroxide	0.387
Allantoin	0.350
Zinc pidolate	0.100
EDTA disodium salt	0.08
Ascorbyl palmitate	0.05
Propyl gallate	0.02
Water	65.013
Total	100.000

Example 2

CREAM

Complexes of proanthocyanidins from Vitis vinifera with phospholipids	0.100
Glycyrrhetinic acid	0.800
Telmesteine	0.100
Octyl palmitate	7.000
Pentylene glycol	5.000
Karité butter	4.000
Arachidyl alcohol, behenyl alcohol, C 12-20 alkylglucoside	4.000
Glyceryl stearate and glyceryl (100) OE stearate	3.000
Squalene	2.000
Oenothera oil	2.000
Capriloyl glycine	1.500
Bisabolol	1.200
Vitamin E acetate	1.000
Carbomer	0.700
Octyl glycerin	0.600
Sodium hydroxide	0.387
Zinc pidolate	0.100
EDTA disodium salt	0.08
Ascorbyl palmitate	0.05
Propyl gallate	0.02
Water	66.013
Total	100.000

Example 3

CREAM

Complexes of proanthocyanidins from Vitis vinifera with phospholipids	0.100
Glycyrrhetinic acid	0.800
Telmesteine	0.010
Dub po	7.000
Hydrolite-5	5.000
Karitè butter	4.000
Montanov 202	4.000
Arlacel 165	3.000
Squalene ex	2.000
Oenothera oil	2.000
Lipacide C8G	1.500
Bisabolol	1.200
Vitamin E acetate	1.000
Carbopol ultrez 10	0.700
Sensiva SC 50	0.600
Octopirox	0.500
Sodium hydroxide drops P.P.A	0.387
Allantoin	0.350
Nipaguard DMDMH	0.300
Zincidone	0.100
EDTA disodium salt	0.080
Ascorbyl palmitate	0.050
Propyl gallate	0.020
Water	65.303
Total	100.000

Example 4

CREAM

Complexes of proanthocyanidins from *Vitis vinifera* with phospholipids	0.100
Glycyrrhetinic acid	0.800
Telmesteine	0.010
Dub po	7.000
Hydrolite-5	5.000
Karitè butter	4.000
Montanov 202	4.000
Arlacel 165	3.000
Squalene ex	2.000
Oenothera oil	2.000
Lipacide C8G	1.500
Bisabolol	1.200
Vitamin E acetate	1.000
Carbopol ultrez 10	0.700
Sensiva SC 50	0.600
Salicylic acid	0.500
Octopirox	0.500
Sodium hydroxide drops P.P.A	0.465
Allantoin	0.350
Nipaguard DMDMH	0.300
Zincidone	0.100
EDTA disodium salt	0.080
Ascorbyl palmitate	0.050
Propyl gallate	0.020
Water	64.725
Total	100.000

Example 5

CREAM

Complexes of proanthocyanidins from *Vitis vinifera* with phospholipids	0.100
Glycyrrhetinic acid	0.800
Telmesteine	0.010
Dub po	7.000
Hydrolite-5	5.000
Karitè butter	4.000
Montanov 202	4.000
Arlacel 165	3.000
Squalene	2.000
Oenothera oil	2.000
Lipacide C8G	1.500
Bisabolol	1.200
Vitamin E acetate	1.000
Carbopol ultrez 10	0.700
Sensiva SC 50	0.600
Octopirox	0.500
Sodium hydroxide drops P.P.A.	0.387
Allantoin	0.350
Nipaguard DMDMH	0.300
Zincidone	0.100
EDTA disodium salt	0.080
Ascorbyl palmitate	0.050
Hyaluronic acid sodium salt	0.030
Propyl gallate	0.020
Water	65.273
Total	100.000

Example 6

CREAM

Complexes of proanthocyanidins from *Vitis vinifera* with phospholipids	0.100
Glycyrrhetinic acid	2.000
Telmesteine	0.010
Ethylhexyl palmitate	9.000
Butyrospermum parkii	6.000
Pentylene glycol	5.000
Butylene glycol	3.000
PEG-100 stearate	1.500
Glyceryl stearate	1.500
Capryloyl glycine	1.500
Arachidyl glucoside	1.360
Arachidyl alcohol	1.320
Behenyl alcohol	1.320
Bisabolol	1.200
Tocopheryl acetate	1.000
Carbomer	0.700
Ethylhexyl glycerin	0.600
Piroctone olamine	0.500
Sodium hydroxide	0.387
Allantoin	0.350
DMDM hydantoin	0.300
Sodium hyaluronate	0.200
Disodium EDTA	0.080
Tetrahexyidecyl ascorbate	0.050
Propyl Gallate	0.020
Water	61.003
Total	100.000

Example 7

CREAM

Complexes of proanthocyanidins from *Vitis vinifera* with phospholipids	0.100
Glycyrrhetinic acid	2.000
Telmesteine	0.010
Ethylhxyl palmitate	9.000
Butyrospermum parkii	6.000
Pentylene glycol	5.000
Butylene glycol	3.000
PEG-100 stearate	1.500
Glyceryl stearate	1.500
Capryloyl glycine	1.500
Arachidyl glucoside	1.360
Arachidyl alcohol	1.320
Behenyl alcohol	1.320
Bisabolol	1.200
Salicylic acid	1.000
Tocopheryl acetate	1.000
Sodium hydroxide	0.785
Carbomer	0.700
Ethylhexylglycerin	0.600
Piroctone olamina	0.500
Allantoin	0.350
DMDM hydantoin	0.300
Disodium EDTA	0.080
Tetrahexyldecyl ascorbate	0.050
Propyl gallate	0.020
Water	59.805
Total	100.000

Example 8

CREAM

Complexes of proanthocyanidins from *Vitis vinifera* with phospholipids	0.100
Glycyrrhetinic acid	2.000
Telmesteine	0.010
Ethylhexyl palmitate	9.000
Butyrospermum parkii	6.000
Pentylene glycol	5.000
Butylene glycol	3.000
PEG-100 stearate	1.500
Glyceryl stearate	1.500
Capryloyl glycine	1.500
Arachidyl glucoside	1.360
Arachidyl alcohol	1.320
Behenyl alcohol	1.320
Bisabolol	1.200
Tocopheryl acetate	1.000
Carbomer	0.700
Ethylhexylglycerin	0.600
Piroctone olamine	0.500
Sodium hydroxide	0.387
Allantoin	0.350
DMDM hydantoin	0.300
Sodium hyaluronate	0.100
Disodium EDTA	0.080
Tetrahexyldecyl ascorbate	0.050
Propyl gallate	0.020
Water	61.103
Total	100.000

The compositions of the present invention showed very good tolerability. They do not contain allergenic substances, derivatives from animal sources (such as lanolin, beeswax, animal fat), preservatives (such as parabens, isothiazolones, phenol derivatives, and the like) which are often responsible for allergic contact dermatitis.

Therefore, thanks to the above mentioned characteristics, the compositions of the present invention are useful for the treatment of already existing skin allergic reactions, for the prevention of recurrent forms, and as adjuvants in the treatment of chronic diseases such as atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis, radiation dermatitis, xerosis and atopia.

More particularly, the compositions of the present invention are useful in the treatment of conditions such as irritative and eczematous dermatitis, as moisturizers and lenitive agents for sensitive, delicate skin; in allergic irritations due to medicaments, detergents, solvents; in erythema due to excessive exposure to sun radiaitons; in case of insect stings, redness of various origin, post-shaving irritations, slight burns, skin hyper-reactivity; as normalizers after esthetic treatments, such as peeling with acid glycolic or laser-therapy.

The excellent tolerability of the compositions of the present invention makes them also suitable in pediatrics.

The present invention also relates to the use of proanthocyanidins for the preparation of a topical medicament for the treatment of skin inflammations, in particular atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis, radiation dermatitis, xerosis, psoriasis and atopia; and of mucosae inflammatory conditions, in particular of vaginal, rectal, eye gingival and buccal mucosae.

CLAIMS

1. The use of proanthocyanidins for the preparation of a topical medicament for the treatment of inflammatory conditions of the skin and mucosae.

2. The use as claimed in claim 1 for the treatment of atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis, radiation dermatitis, xerosis, psoriasis and atopia.

3. The use as claimed in claim 1 for the treatment of inflammatory conditions of the vaginal, rectal, buccal and eye mucosae.

4. The use as claimed in any one of claims 1-3, in which proanthocyanidins are in the form of complexes with phospholipids.

5. The use as claimed in any one of claims 1-4, in which proanthocyanidins are in combination with glycyrrhetinic acid.

6. The use as claimed in any one of claims 1-5, in which proanthocyanidins are further in combination with telmesteine.

7. The use as claimed in any one of claims 1-6, in which proanthocyanidins are further in combination with alpha-bisabolol.

8. The use as claimed in any one of claims 1-7, in which proanthocyanidins are further in combination with piroctone olamine.

9. The use as claimed in any one of claims 1-8, in which proanthocyanidins are further in combination with wetting agents and moisturizers.

10. Pharmaceutical compositions for the topical administration, comprising as active ingredients proanthocyanidins, glycyrrhetinic acid and telmesteine in admixture with a suitable carrier.

11. Pharmaceutical compositions as claimed in claim 10, in the form of cream, gel, lotion, suspension, spray, ointment, foam.

12. Pharmaceutical compositions as claimed in claim 10 or 11, in which the carrier comprises squalene, fatty acids, fatty acids esters, vegetable oils, natural or synthetic triglycerids.

13. Pharmaceutical compositions as claimed in claim 12, in which the carrier comprises squalene, karitè butter, octyl palmitate and oenothera oil.

14. Pharmaceutical compositions as claimed in any one of claims 10-13, further comprising tocopherols, ascorbic acid or esters thereof.

15. Pharmaceutical compositions as claimed in claim 14, comprising tocopherol acetate and ascorbyl palmitate or tetrapalmitate.

16. Pharmaceutical compositions as claimed in any one of claims 10-15, comprising salicylic acid.

17. Pharmaceutical compositions as claimed in any one of claims 10-16, comprising hyaluronic acid.

18. Pharmaceutical compositions as claimed in any one of claims 10-17, further comprising at least one compound selected from alpha-bisabolol, zinc pidolate, allantoin, piroctone olamine.

19. Pharmaceutical compositions as claimed in any one of claims 10-18, in which the active ingredients are present in the following concentrations:

a) proanthocyanidins in the form of complexes with phospholipids: 0.01% to 1%;

b) glycyrrhetinic acid: 0.1 to 5%;

c) telmesteine: 0.01% to 1%.

20. Compositions as claimed in claim 19 in which glycyrrhetinic acid is present in concentrations ranging from 1 to 2%.

21. A method of treatment of patients affected with skin and mucosae inflammatory conditions, which comprises the topical administration of an effective amount of proanthocyanidins.

22. A method as claimed in claim 21 for the treatment of atopic dermatitis,

allergic contact dermatitis, seborrheic dermatitis, radiation dermatitis, xerosis, psoriasis and atopia.

23. A method as claimed in claim 21 or 22 which further comprises the topical administration of telmesteine.

24. A method as claimed in claim 21, 22 or 23 which further comprises the topical administration of glycyrrhetinic acid.

25. A method as claimed in any one of the claims 21-24 which further comprises the topical administration of one or more agents selected from salicylic acid, allantoin, hyaluronic acid, zinc pidolate, alpha-bisabolol, piroctone olamine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03329

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61K31/425 A61P17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1995, no. 03, 28 April 1995 (1995-04-28) & JP 06 336421 A (KOSE CORP;OTHERS: 01), 6 December 1994 (1994-12-06) cited in the application abstract ---	1,3,5, 21,24
P,X	DE 101 31 641 A (SCHWABE WILLMAR GMBH & CO) 27 June 2002 (2002-06-27) claims 1,14,18 ---	1,2,21, 22
P,X	EP 1 256 335 A (COGNIS FRANCE S A) 13 November 2002 (2002-11-13) page 16, line 4,5; claims 1,2,10,12; table 6 --- -/--	1,2,21, 22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2003	03/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ESTANOL, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 698 360 A (MASQUELIER JACK) 6 October 1987 (1987-10-06) column 6, line 9-11	1,21
X	EP 0 694 305 A (INDENA SPA) 31 January 1996 (1996-01-31) cited in the application claims 1,2,5,8; example 1	2,22
A	EGGENSPERGER H: "ACTIVE COMPLEXES FOR SMOOTH SKIN NATURE COMBATS OXIDATIVE STRESS WIRKSTOFFKOMPLEXE FUER GLATTE HAUT NATUR GEGEN OXIDATIVEN STRESS" COSSMA: COSMETICS, SPRAY TECHNOLOGY, MARKETING, BRAUN FACHVERLAGE, KARLSRUHE, DE, vol. 2, no. 8, August 2001 (2001-08), pages 38-39, XP008016527 ISSN: 1439-7676 the whole text	1-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/03329

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/03329

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